

CARDIOVASCULAR MEDICINE AND SOCIETY

A Comparative Analysis of Current Lipid Treatment Guidelines

Nothing Stands Still



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ABSTRACT

Lipid treatment guidelines have continued to evolve as new evidence emerges. We sought to review similarities and differences of 5 lipid treatment guidelines from the American College of Cardiology/American Heart Association, Canadian Cardiovascular Society, European Society for Cardiology/European Atherosclerosis Society, U.S. Preventive Services Task Force, and U.S. Veterans Affairs/Department of Defense. All guidelines utilize rigorous evidentiary review, highlight statin therapy for primary and secondary prevention of atherosclerotic cardiovascular disease, and emphasize a clinician-patient risk discussion. However, there are differences in statin intensities, use of risk estimators, treatment of specific patient subgroups, and consideration of safety concerns. Clinicians should understand these similarities and differences in current and future guideline recommendations when considering if and how to treat their patients with statin therapy. (J Am Coll Cardiol 2018;71:794–9) © 2018 by the American College of Cardiology Foundation.

With lipid guidelines, as with history, “nothing stands still” (1). Through completion of large-scale randomized controlled trials, high-quality clinical evidence emerges that drives changes in major guidelines. We sought to clarify similarities and differences to improve clinicians’ critical sense of lipid guidelines as they evolve.

We considered 5 guidelines on the treatment of hypercholesterolemia recently published by high-profile cardiovascular societies: 2014 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2); 2016 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult (3); 2016 European Society for Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias (4); 2016 U.S. Preventive Services Task Force (USPSTF) report, Statin Use for the

Primary Prevention of Cardiovascular Disease in Adults (5,6); and 2014 U.S. Department of Veteran Affairs–U.S. Department of Defense (VA-DoD) Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction (7) (Central Illustration).

GUIDELINES EVIDENTIARY PROCESSES

The guidelines were drafted and verified by panels comprising experts in the field. The ACC/AHA and VA-DoD utilized 2 distinct panels for evidentiary review and guideline composition, whereas the CCS, ESC/EAS, and USPSTF employed single working groups to review evidence and draft the guidelines. Committees used a strict evidentiary review process. For example, the ACC/AHA considered only randomized control trials (RCTs), systematic reviews of randomized control trials, and meta-analyses that were rated fair to good by an independent contractor. Poorly rated studies were excluded. The USPSTF and



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VA-DoD described the use of RCTs and systematic reviews of RCTs, although without discussion of explicitly excluding poorly rated studies. Although the CCS and ESC/EAS used a strict analysis of the published data and cited references for recommendations, they did not state limitations on the types of papers used (Table 1).

The purview of all guidelines except for the USPSTF (primary prevention only) encompasses primary and secondary atherosclerotic cardiovascular disease (ASCVD) prevention. Each guideline describes varying certainty for each recommendation, as well as the strength of evidence to support it. For example, the ACC/AHA and ESC/EAS writers provide Classes of Recommendation (I, IIa, IIb, and III) and Levels of Evidence (A to C). VA-DoD uses “high,” “moderate,” “low,” and “very low” to describe quality of evidence, and recommendations are either “strong” or “weak” and “for” or “against.”

The ethos of each writing committee is essentially similar, with expert and rigorous review, inclusion of high-quality published data, and consensus generation in drafting the recommendations; however, there are varying degrees of transparency disclosed in each guideline. This does not necessarily affect the validity of each guideline, but can affect the level of debate surrounding the more contentious recommendations.

RISK ESTIMATORS AND PRIMARY PREVENTION

Each guideline makes recommendations on statin therapy for primary prevention using various estimators for 10-year risk of ASCVD events. The ACC/AHA and USPSTF recommend the use of the ACC/AHA Pooled Cohort Risk Equations, whereas the CCS recommends use of the Framingham Risk Score (FRS), and VA-DoD suggests the use of either mechanism. The ESC/EAS recommend use of the Systemic Coronary Risk Evaluation (SCORE) estimator.

Risk estimators are derived from large studies in the United States or Europe. All include age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and systolic blood pressure as predictors. However, ethnicity, treatment for hypertension, diabetes, and smoking status are only included in some; thus, patient risk may vary with different estimators (Table 2).

Outcomes are different between risk estimators. Outcome for the FRS is the most inclusive, predicting 10-year risk of coronary heart disease, cerebrovascular events, peripheral artery disease, or heart failure. The ACC/AHA Pooled Cohort Risk Equations are restrictive, predicting 10-year risk for first hard ASCVD event, defined as coronary heart disease death, nonfatal

myocardial infarction (MI), or stroke. The SCORE estimator is most specific, predicting 10-year risk of first fatal atherosclerotic event, including MI, stroke, other occlusive arterial disease, or sudden cardiac death. These differences in outcome measures are important when considering differences in treatment thresholds between the guidelines.

Thresholds for which treatment is recommended range between 5% and 20% 10-year risk of ASCVD. The lowest threshold is from the ESC/EAS, which recommends statin treatment for patients with 5% to 10% 10-year ASCVD risk and LDL-C ≥ 100 mg/dl. ESC/EAS recommends use of the SCORE risk estimator, which has the strictest outcome by predicting risk of only fatal events. The highest threshold for treatment is $\geq 20\%$ 10-year ASCVD risk using the FRS estimator, which predicts risk of the broadest outcomes. The ACC/AHA, USPSTF, and VA-DoD recommend treatment at thresholds of $\geq 7.5\%$, $\geq 10\%$, and $\geq 12\%$ 10-year risk of ASCVD respectively, using the ACC/AHA Pooled Cohort Risk Equations. Of note, all of the guidelines recommend treatment for patients with LDL-C ≥ 190 mg/dl.

Despite the wide range in treatment thresholds between the guidelines, the number of patients for which statin treatment is recommended or considered is likely similar given the differences in outcomes in the risk estimators. Of adults age 40 to 65 years, a comparative analysis estimated the ACC/AHA and ESC/EAS guidelines respectively recommend statin treatment in 43.8% versus 39.1% in the United States and 49.9% versus 47.6% in Poland (8). In other words, a 7.5% risk derived from one risk estimator may be equivalent to a 10% risk from another, depending on outcomes predicted by each. This suggests that individuals for whom statin therapy is recommended or should be considered for primary prevention may ultimately not differ greatly amongst guidelines, and highlights the importance of the clinical-patient risk discussion.

TREATMENT RECOMMENDATIONS

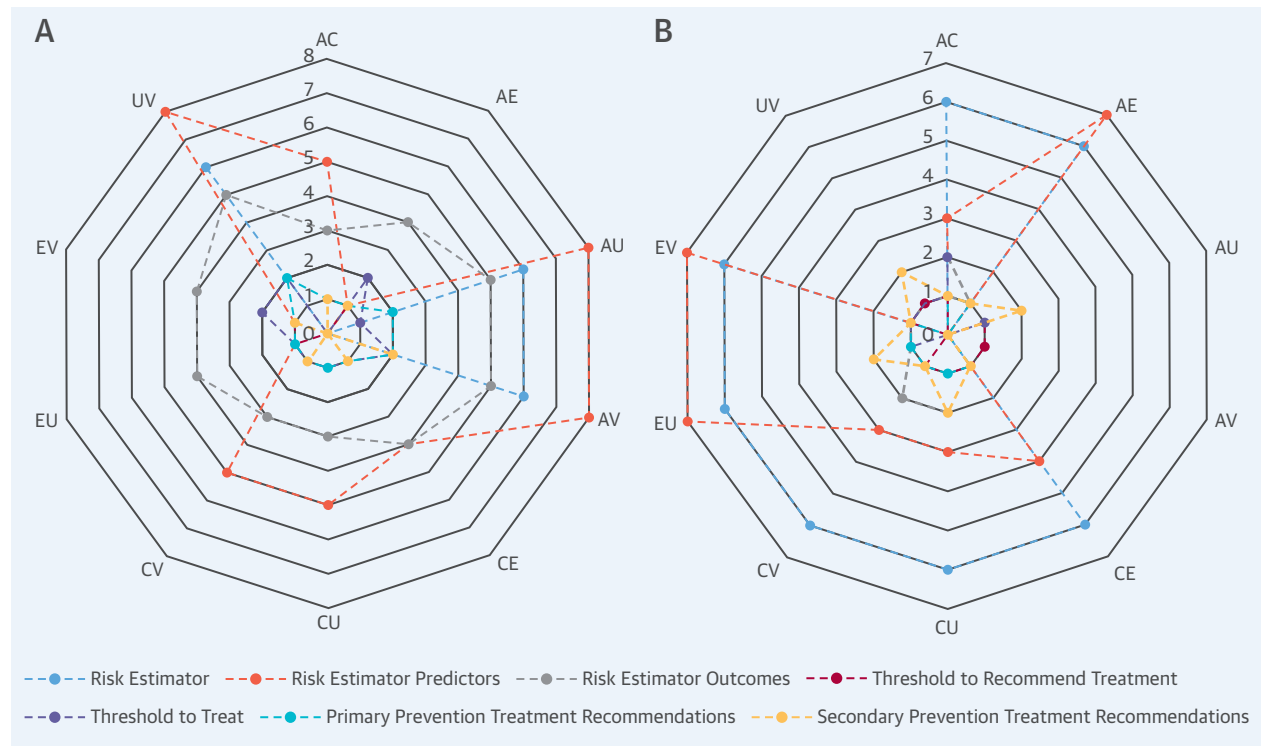
The guidelines highlight the importance of lifestyle prior to and in conjunction with pharmacotherapy for reducing the risk of ASCVD. The components of lifestyle emphasized include heart-healthy diets, reducing excessive weight, avoidance of tobacco, and physical activity.

Statins are the recommended initial pharmacotherapy, but differ between guidelines in intensity or dose of therapy. The CCS focuses on a targeted

ABBREVIATIONS AND ACRONYMS

ACC	= American College of Cardiology
AHA	= American Heart Association
ASCVD	= atherosclerotic cardiovascular disease
CCS	= Canadian Cardiovascular Society
CHD	= coronary heart disease
EAS	= European Atherosclerosis Society
ESC	= European Society of Cardiology
FRS	= Framingham Risk Score
MI	= myocardial infarction
SCORE	= Systemic Coronary Risk Evaluation
USPSTF	= U.S. Preventive Services Task Force
VA-DoD	= Veterans' Affairs-Department of Defense

CENTRAL ILLUSTRATION Similarities and Differences Among 5 Major Cholesterol Guidelines Regarding Statin Therapy



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We assigned weighted scores to each categorical variable and plotted the comparison of each between the guidelines on a linkage graph. **(A)** The degree of similarity (i.e., the points in which the guidelines were concordant) is represented by the higher numerical score and longer distance from the center of the plot. **(B)** The degree of difference (i.e., the aspects in which the guidelines are the most discordant) is represented by longer lines and distance from the center of the plot. Comparator groups: A = American College of Cardiology/American Heart Association; C = Canadian Cardiovascular Society; E = European Society for Cardiology/European Atherosclerosis Society; U = U.S. Preventive Services Task Force; V = Veterans Affairs-Department of Defense (e.g., AC = comparison between the American College of Cardiology/American Heart Association and Canadian Cardiovascular Society).

TABLE 1 Evidentiary Process for Guideline Recommendations

	ACC/AHA	CCS	ESC/EAS	USPSTF	VA/DoD
Committee composition	Independent bodies for evidence review AND guideline composition	Single working group to review evidence and draft guidelines	Single working group to review evidence and draft guidelines	Single working group to review evidence and draft guidelines	Independent bodies for evidence review AND guideline composition
Literature included	RCTs, systemic reviews of RCTs, and meta-analyses rated fair to good. Excluded poorly reviewed RCTs	Does not specify the literature included in methods	Does not specify the literature included in methods	RCTs and systematic reviews of RCTs	RCTs and systematic reviews of RCTs
Description of Recommendations	<ul style="list-style-type: none"> Class of Recommendations I, IIa, IIb, or III Level of Evidence A-C 	<ul style="list-style-type: none"> Grade of Recommendation "strong" or "conditional" Level of Evidence "high" to "very low" 	<ul style="list-style-type: none"> Class of Recommendations I, IIa, IIb, or III Level of Evidence A-C 	<ul style="list-style-type: none"> Grade of Recommendation A-D or I Level of Evidence "high" to "low" 	<ul style="list-style-type: none"> Strength of Recommendation "for" or "against" and "strong" or "weak" Level of Evidence "high" to "very low"

Comparison of similarities and differences of evidentiary process between guidelines.
 ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society for Cardiology/European Atherosclerosis Society; RCT = randomized control trial; USPSTF = U.S. Preventive Services Task Force; VA/DoD = Veterans Affairs/Department of Defense.

TABLE 2 Guideline Recommendations for Primary and Secondary Prevention of ASCVD

	ACC/AHA	CCS	ESC/EAS	USPSTF	VA-DoD
Primary Prevention of Clinical ASCVD					
Recommended risk estimator	ACC/AHA pooled cohort risk equations	Framingham Risk Score	Systemic coronary risk evaluation	ACC/AHA pooled cohort risk equations	ACC/AHA pooled cohort risk equations OR Framingham Risk Score
Risk estimator predictors	Age, sex, ethnicity, TC, HDL-C, systolic blood pressure, treatment for hypertension, and diabetes	Age, sex, TC, HDL-C, systolic blood pressure, treatment for hypertension, smoking status, and diabetes	Age, sex, smoking status, systolic blood pressure, TC, and HDL-C	Age, sex, ethnicity, TC, HDL-C, systolic blood pressure, treatment for hypertension, and diabetes	See other columns
Risk estimator outcomes	10-yr risk of first hard ASCVD event (coronary heart disease death, nonfatal MI, or stroke)	10-yr risk of coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure	10-yr risk of first fatal atherosclerotic event (MI, stroke, other occlusive arterial disease, or sudden cardiac death)	10-yr risk of first hard ASCVD event (coronary heart disease death, nonfatal MI, or stroke)	See other columns
Threshold to recommend treatment	<ul style="list-style-type: none"> ≥ 7.5% 10-yr risk for age 40-75 years LDL-C ≥ 190 mg/dl for age ≥ 21 yrs 	<ul style="list-style-type: none"> ≥ 20% 10-yr risk for age 40-75 yrs LDL-C ≥ 193 mg/dl 	<ul style="list-style-type: none"> ≥ 10% 10-yr risk AND LDL-C ≥ 70 mg/dl OR 5%-10% 10-yr risk AND LDL-C ≥ 100 mg/dl for age 40-65 yrs 	<ul style="list-style-type: none"> ≥ 10% 10-yr risk (need 1 additional ASCVD risk factor*) for age 40-75 yrs 	<ul style="list-style-type: none"> ≥ 12% 10-yr risk for age men > 35 and women > 45 yrs LDL-C > 190 mg/dl
Threshold to consider treatment	<ul style="list-style-type: none"> 5%-7.5% 10-yr risk for age 40-75 yrs 	<ul style="list-style-type: none"> 10%-19% 10-yr risk for age 40-75 yrs 	<ul style="list-style-type: none"> ≥ 10% 10-yr risk AND LDL-C < 70 mg/dl OR 5%-10% 10-yr risk AND LDL-C ≥ 70 mg/dl OR 1%-5% 10-yr risk AND LDL-C ≥ 100 mg/dl for age 40-65 yrs 	<ul style="list-style-type: none"> 7.5%-10% 10-yr risk for age 40-75 yrs LDL-C ≥ 190 mg/dl 	<ul style="list-style-type: none"> 6%-12% 10-yr risk for age men > 35 and women > 45 yrs
Treatment recommendations	<ul style="list-style-type: none"> Lifestyle ≥7.5% 10-yr ASCVD risk: moderate or high intensity statin 5%-7.5% risk: moderate intensity <5% OR age <40 or >75 yrs and LDL-C <190 mg/dl: considered in select patients Clinician-patient risk discussion prior to statin initiation 	<ul style="list-style-type: none"> Lifestyle Target ≥50% reduction in LDL-C OR LDL-C <77 mg/dl Clinician-patient risk discussion prior to statin initiation 	<ul style="list-style-type: none"> Lifestyle Maximally tolerated dose of statin to achieve target treatment goal Clinician-patient risk discussion prior to statin initiation 	<ul style="list-style-type: none"> Lifestyle >10% ASCVD 10-yr risk: low-moderate statin dose 7.5%-10% 10-yr risk: low-moderate dose for select patients Clinician-patient risk discussion prior to statin initiation 	<ul style="list-style-type: none"> Lifestyle >12% 10-yr ASCVD risk: moderate-dose statin 6%-12% 10-yr risk: moderate-dose statin for select patients Clinician-patient risk discussion prior to statin initiation
Secondary Prevention (for Patients With Clinical ASCVD)					
Treatment recommendations	<ul style="list-style-type: none"> ≤75 yrs AND without contraindications or safety concerns: high-intensity statin >75 yrs OR with contraindications or safety concerns (irrespective of age): moderate-intensity statin 	<ul style="list-style-type: none"> Target ≥50% reduction in LDL-C OR LDL-C <77 mg/dl If LDL-C ≥193 mg/dl, target ≥50% reduction in LDL-C 	Maximally tolerated dose of statin to achieve target treatment goal	Guideline recommendations for primary prevention only. No recommendations for secondary prevention.	<ul style="list-style-type: none"> Moderate-dose statin for patients with ASCVD High-dose statin for select patients (e.g. ACS, multiple uncontrolled risk factors, recurrent CV events)

Comparison of similarities and differences between guidelines for primary and secondary prevention of atherosclerotic cardiovascular disease. *Dyslipidemia, diabetes, hypertension, or smoking. ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; other abbreviations as in Table 1.

reduction in LDL-C level without discussion of statin intensity or dose. Similarly, the ESC/EAS uses absolute LDL-C levels as a treat-to-target goal. The ACC/AHA, USPSTF, and VA-DoD recommend statin intensity or dose based on clinical profiles. The ACC/AHA employs statin *intensity* in LDL-C reduction, which is delineated into high-, moderate-, and low-intensity categories targeting a reduction in LDL-C ≥50%, 30% to 50%, and <30%, respectively. The USPSTF and VA-DoD suggest *dosage* of statin for LDL-C reduction. In both guidelines, high-, moderate-,

and low-dose statins reflect the same categorization as high-, moderate-, and low-intensity statins as the ACC/AHA. We believe “intensity” is the most appropriate terminology for guidelines, because similar doses of different statins may have different intensities as defined as level of LDL-C reduction. The guidelines suggest considering nonstatin therapies for patients with statin intolerance or inadequate therapeutic response on statin therapy. However, lesser quality of evidence leads to relatively weaker recommendations at this time.

TABLE 3 Guideline Recommendations for Special Groups and Safety Concerns

	ACC/AHA	CCS	ESC/EAS	USPSTF	VA/DoD
Elderly (age >75 yrs or life expectancy <5 yrs)	<ul style="list-style-type: none"> Continue statin if already tolerating 1° prevention: recommend not starting statins for primary prevention. Statin therapy may be considered in selected individuals. 2° prevention: start moderate-intensity statin 	<ul style="list-style-type: none"> If considered HIGH risk, recommend patient and physician discussion to initiate statin therapy 	<ul style="list-style-type: none"> 1° prevention: if risk factors for ASCVD, consider starting statin 2° prevention: treatment same as younger patients, but start at lower dose 	Insufficient evidence to initiate statin for primary prevention	Therapy based on comorbidities, quality of life, and patients' preferences, values, and culture
Diabetes mellitus	Continue or start statin for: <ul style="list-style-type: none"> LDL-C 70-189 mg/dl for age 40-75 yrs If 10-yr ASCVD risk \geq 7.5%, a high intensity statin is reasonable 	Statin therapy for: <ul style="list-style-type: none"> Age \geq 40 yrs Age \geq 30 yrs and duration of disease > 15 yrs Microvascular complications 	Statin therapy for: <ul style="list-style-type: none"> LDL-C \geq 100 mg/dl OR LDL-C 70-100 mg/dl AND end-organ damage OR 1 additional ASCVD risk factor* 	<ul style="list-style-type: none"> Recommend statin for \geq10% 10-yr risk Consider statin for 7.5%-10% 10-yr risk 	Recommend statin if hypertension and/or smoking present
End-stage renal disease	Maintenance dialysis: no recommendation for or against use of statins	<ul style="list-style-type: none"> Not to initiate therapy in dialysis-dependent patients Continue therapy in those ALREADY receiving it at time of dialysis initiation 	No recommendations	No recommendations	Therapy based on comorbidities, quality of life, and patients' preferences, values, and culture
Other groups	<ul style="list-style-type: none"> Solid organ transplantation and HIV: caution with drug-drug interactions Rheumatologic and inflammatory diseases: use clinician judgement 		<ul style="list-style-type: none"> Solid organ transplantation: Caution with drug-drug interactions, start at lower dose HIV: consider as high-risk patients Rheumatologic and inflammatory diseases: use clinician judgement Mental disorder: consider as high-risk patients, attention to lifestyle and medication adherence 		
Safety concerns:	<ul style="list-style-type: none"> Impaired renal or hepatic function Unexplained ALT elevation \geq3\timesupper limits of normal Elderly Concomitant drugs that alter statin metabolism Previous statin intolerance or muscle disorders Asian ancestry 		<ul style="list-style-type: none"> Impaired renal function Asian ancestry Polypharmacy Multiple comorbidities 		

Comparison of similarities and differences between guidelines for special groups and safety concerns. *Dyslipidemia, hypertension, or smoking. ALT = alanine transaminase; HIV = human immunodeficiency virus; other abbreviations as in Table 1.

PRIMARY PREVENTION. The ACC/AHA, USPSTF, and VA-DoD recommend different intensities or dosages of statins for primary prevention based on 10-year risk thresholds. The ACC/AHA recommends using a moderate- or high-intensity statin (in patients with \geq 7.5% 10-year ASCVD risk). The USPSTF and VA-DoD recommend either a low- or moderate-dose statin without use of a high-dose statin in any cohort. As discussed, the CCS and ESC/EAS use treatment goals to determine selection and dosing of statins. Importantly, all guidelines recognize the importance of shared decision-making and emphasize a clinician-patient risk discussion.

SECONDARY PREVENTION. The ACC/AHA and VA-DoD recommend varying intensities or doses of statins for secondary prevention in patients with

ASCVD. The ACC/AHA recommends high-intensity statins for patients age \leq 75 years without contraindications and moderate-intensity statins for the other groups. The VA-DoD recommends a moderate-dose statin for most patients with ASCVD and a high-dose statin for select patients deemed to be at high risk for future events. The CCS and ESC/EAS again use treatment goals to determine statin selection and dosing.

SPECIAL GROUPS

ELDERLY PATIENTS. All guidelines suggest statin use in the elderly (defined as age >75 years or life expectancy <5 years) as a point of uncertainty. The ACC/AHA recommends continuing a statin if already tolerating, recommends not starting one for primary

prevention, and recommends initiating a moderate-intensity statin for secondary prevention. The ESC/EAS considers initiating a statin for primary prevention if ASCVD risk is particularly high, although it recommends a lower starting dose of statin and gradual titration to reach the target, given altered pharmacokinetics in the elderly. The CCS recommends a physician-patient discussion in high-risk patients, and the VA-DoD employs a decision based on comorbidities, quality of life, patient preferences, values, and culture. The USPSTF indicates that there is insufficient evidence to recommend statin initiation in the elderly.

END-STAGE RENAL DISEASE. The ACC/AHA makes no specific recommendations for or against the initiation or discontinuation of statins in end-stage renal disease patients on maintenance hemodialysis. The VA-DoD leaves it as a treatment decision based on patient comorbidities, quality of life, preferences, values, and culture. The CCS explicitly instructs not to initiate therapy in dialysis-dependent patients, but to continue statin therapy in those already receiving it at the time of dialysis initiation.

OTHER GROUPS. The ACC/AHA and ESC/EAS mention solid organ transplantation and patients with human immunodeficiency virus, recommending caution with drug-drug interactions (particularly cyclosporine) and potential initiation at lower doses with careful titration. The ACC/AHA and ESC/EAS suggest clinical judgement in statin initiation with rheumatologic and inflammatory diseases given insufficient evidence. ESC/EAS highlights patients with psychiatric disorders as a barrier to medication compliance.

The various guidelines treat these special groups with uncertainty in statin usage because of the lack of rigorous data that show significant and unequivocal benefit or harm.

SAFETY CONCERNS

Often overlooked, safety and monitoring are critical for appropriate statin use (Table 3). The ACC/AHA and ESC/EAS both recommend routine monitoring. They recommend caution with appropriate dose reductions in patients with impaired renal or hepatic function, patients with unexplained alanine transaminase elevation $\geq 3\times$ the upper limit of normal, elderly patients, patients taking concomitant drugs that alter statin metabolism, those with a history of previous statin intolerance or muscle disorders, and patients of Asian ancestry.

CONCLUSIONS

We undertook a comparative analysis of 5 major lipid treatment guidelines. We found a high degree of consensus in recommendations. All utilize a rigorous evidentiary process emphasizing statins for primary/secondary prevention. Moreover, all recommend joint decision-making with a clinician-patient discussion. However, there are differences. Recommendations on statin intensity, on patients with particular comorbidities, and addressing safety concerns vary among the guidelines. Furthermore, the utilization of differing risk estimators requires an a priori understanding of compounding comorbidities and their influence on pre-test probability of ASCVD. The incorporation of new high-quality data could help resolve some of these differences. Clinicians can look forward to improved resolution of areas where treatment decisions diverge as evidence-based recommendations evolve. Nothing stands still.

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KEY WORDS atherosclerotic cardiovascular disease, cholesterol, lipid, primary prevention, secondary prevention, statin